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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/500,397	02/08/2000	Gerald Soff	4228-1-1-1	2549

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/500,397	SOFF ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-21,23,24 and 76-90* is/are pending in the application.

4a) Of the above claim(s) *78, 87* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-21, 23-24, 76-77, 79-86, 88-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 19-21, 23-24, 76-77, 79-86, 88-90, a method for treating angiogenic disease, in particular hemangiomas, are being examined. Claims 78, 87 are withdrawn from consideration as being drawn to non-elected inventions.

The following are the remaining rejections.

DOUBLE PATENTING

Applicant is reminded that that the double patenting rejection remains for the reasons of record, and is maintained.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Rejection under 35 USC 112, first paragraph of claims 19-21, 23-24, 76-77, 79-86, 88-90, pertaining to lack of enablement for a method for treating angiogenic disease, in particular hemangiomas, remains for reasons already of record in paper of 10/20/04.

It is noted that Applicant's submission of a second Supplemental Declaration by Dr. Gerald Soff in the response is acknowledged and entered.

Applicant recites in re Wands, and argues that the Examiner has not made an enablement rejection over the method as a whole, but based on an analysis of only one of the factors while ignoring one or more of the others.

Contrary to Applicant's arguments, all the factors in Wands analysis has been taken into consideration in previous rejections, and in the present Office action.

1) Concerning the Breadth of the Claims and Nature of the Invention, the scope of the claims is overly broad, encompassing a method for treating any angiogenic disease, including hemangiomas, comprising administering an effective amount of a plasminogen activator.

The specification however only discloses that a small amount of angiostatin is detected in cancer patients administered with a plasminogen activator. In addition, the presently submitted Second Supplemental Declaration only discloses that **affinity purified** angiostatin (emphasis added) produced in *ex vivo* plasma in the presence of a a plasminogen activator could be used for administering into mice for successful treatment of hemangiomas, a benign growth with dilated blood vessel.

It is noted however that **the second Supplemental Declaration is not commensurate with the scope of the claimed invention. No plasminogen activator was actually administered into mice to successfully treat hemangiomas, and that the data in the Supplemental Declaration at most reinforces what has been well known in the art that isolated angiostatin could be used to treat some angiogenic diseases.**

2) Concerning the State of the Art and the Level of Skill in the Art, the Examiner takes note that although the step of administrating a plasminogen activator is routine in the art, however, the art does not know which amount of plasminogen activator is to be

administered such that an adequate amount of angiostatin would be produced for successful treatment of any angiogenic diseases, including hemangiomas.

3) Concerning the level of predictability in the Art, the level of unpredictability is very high in the instant application. **One cannot predict which amount of plasminogen activator to be administered is effective for treating any angiogenic diseases, including hemangiomas, nor whether an effective, adequate amount of angiostatin could be produced by increasing the amount of an administered plasminogen activator, such that angiogenesis, or generation of new blood vessels, in angiogenic diseases, including hemangiomas, could be successfully treated, in view of the vascularization effect of the plasminogen activator, as taught by Berman et al, of record.**

Applicant argues that the amount of plasminogen activator administered is a therapeutically effective amount that increases the amount of angiostatin in the animal, and is not an amount that does not promote vascularization, nor an amount that would be effective for canceling the effect of vascularization, nor an amount that would produce an adequate amount of angiostatin effective for treating any angiogenic diseases in the presence of the vascularization effect by the plasminogen activator per se, as required by the Examiner.

Applicant argues that one can increase the amount of angiostatin in an animal to treat an angiogenic disease, such as hemangiomas. Applicant argues that the amount of plasminogen activator administered is sufficient to cause conversion of plasminogen

to plasmin, which is then converted to angiostatin in the presence of endogenous sulhydryl donors.

Applicant submit a second supplemental Declaration by Dr. Gerald A Soff. Applicant argues that the Declaration of 02/13/02, the supplemental Declaration of 12/04/01 and the present second supplemental Declaration show that administration of a therapeutically effective amount of a plasminogen activator alone increases the amount of angiostatin in an animal, and induces anti-angiogenic activity in the animal (Declaration, para 17-19 and Exhibits D and E).

In the present second Supplemental Declaration, which is not commensurate with the scope of the claimed invention, it is shown that a plasminogene activator alone is effective to generate angiostatin in *ex vivo* plasma of a normal human , in the presence of a sulhydryl donor (Item A, paragraphs 8-12). The present Declaration further shows that the **affinity-purified** (emphasis added) human angiostatin generated in the above ex vivo plasma reduces hemangiomas tumor volume, and avoided the onset of splenomegaly and hematological complications (Item B, paragraphs 13-22).

Applicant's arguments set forth in paper of 08/24/04 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that in the second Supplemental Declaration, no plasminogen activator was actually administered into mice to successfully treat hemangiomas. Only affinity purified angiostatin produced in isolated plasma of a normal human from a plasminogen activator is administered into mice having hemangiomas, wherein the concentration of the isolated angiostatin to be administered could be readily adjusted, and wherein the

vascularization effect of plasminogen activator is absent. The data in the Supplemental Declaration at most reinforces what has been well known in the art that isolated angiostatin could be used to treat some angiogenic diseases.

It is further noted that although the original Declaration dated 02/13/01 and the first Supplemental Declaration dated 12/04/01, all submitted on 04/17/03, show that some cancers could be treated by administrating a plasminogen activator, one cannot extrapolate the treatment of some cancers to treatment of any angiogenic diseases, i.e. a disease caused by generation of new blood vessels into a tissue or organ, e.g. ocular neovascularization, arthritis, and diabetes (WO 97/41824, page 1, last paragraph, of record), because different diseases have different characteristics and are not expected to response to the same drug, especially in view that a plasminogen activator, urokinase, has been shown to have an opposite effect of angiostatin, i.e. inducing vascularization in vivo, as taught by Berman et al, of record.

Applicant has not taught that a plaminogen activator is effective in treating any angiogenic diseases, and in particular hemangiomas, a benign growth with dilated blood vessel. Treating angiogenic diseases, including hemangiomas, using a plasminogen activator, however is unpredictable, in view of the teaching of Berman et al (of record) that a plasminogen activator, urokinase, actually promotes vascularization of the cornea in vivo, which has an opposite effect of angiostatin.

One cannot predict which amount of plasminogen activator does not promote vascularization, an opposite effect of angiostatin, nor which amount of plasminogen activator would be effective for cancelling the effect of vascularization, nor which

amount of plasminogen activator would produce an adequate amount of angiostatin effective for treating any angiogenic diseases, in particular hemangiomas, in the presence of the vascularization effect by the plasminogen activator per se.

Further, although angiostatin per se inhibits angiogenesis in cornea, or affinity-purified angiostatin produced from ex vivo plasma could reduces the volume of hemangiomas in mice, the claims are not drawn to a method for treating angiogenic diseases, or hemangiomas, using angiostatin per se, or a method for inhibiting angiogenesis in cornea, using angiostatin per se.

Further, even if angiostatin is produced in patients with any angiogenic diseases, including hemangiomas, and even if the amount of administered plasminogen activator could be increased, it is unpredictable that the amount of angiostatin produced in patients with angiogenic diseases would be adequate, and/or would not be masked or encountered by the vascularization effect of the plasminogen activator, such urokinase, supra, especially in view that the level of angiostatin detected in plasma of cancer patients treated with urokinase is barely noticeable, as shown in figure 17A, and figure 17A legend on page 9 in the specification, and that the level of angiostatin needed to inhibit a neovascular response to a hydron pellet *in vivo* is 10 ug/ml as shown in figure 5B legend, p.6, in the specification.

In summary, one cannot predict which amount of plasminogen activator to be administered is effective for treating any angiogenic diseases, including hemangiomas, nor whether an effective, adequate amount of angiostatin could be produced in the treated patients, even with a maximum increase in the amount of administered

plasminogen activator, such that any angiogenic diseases, including hemangiomas are successfully treated, in the presence of the vascularization effect of plasminogen activator, as taught by Berman et al, of record.

4) Concerning the amount of direction provided by the Inventor, the guidance is insufficient. Although one can increase the amount of plasminogen activator to be administered, the specification does not disclose whether an effective amount of angiostatin could be obtained by increasing the amount of administered plasminogen, to successfully treat any angiogenic diseases, including hemangiomas.

The specification provides insufficient guidance with regard to the issues discussed above and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success.

5-6) Concerning the Existence of working examples and the Quantity of experimentation needed, other than treatment of some cancers, no working examples for successful treatment of any angiogenic diseases, by administering a plasminogen activator, are provided, and it would be undue experimentation for one of skill in the art to practice the claimed invention in view of the teaching in the art, supra.

Applicant argues that the present invention requires the administration of a therapeutically effective amount of a plasminogen activator to increase the total amount of angiostatin in an animal in order to treat an angiogenic disease. Applicant argues that the specification discloses how to determine if angiostatin is generated, how much angiostatin is generated, and the amount of angiostatin required to inhibit angiogenesis.

Applicant's arguments set forth in paper of 08/24/04 have been considered but are not deemed to be persuasive for the following reasons:

Although the specification discloses how to determine if angiostatin is generated, how much angiostatin is generated, and the amount of angiostatin required to inhibit angiogenesis, however, the specification does not provide disclosure of which amount of plasminogen activator would generate an effective, adequate amount of angiostatin in vivo to inhibit angiogenesis, in the presence of the vascularization effect of a plasminogen activator. Further, although one can increase the amount of plasminogen activator to be administered, the specification does not disclose whether an effective amount of angiostatin could be obtained by increasing the amount of administered plasminogen, such that any angiogenic diseases, including hemangiomas would be successfully treated.

The specification provides insufficient guidance with regard to the issues discussed above and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the

invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Thus, although an example is not always required, however, given 1) the unpredictability of treating any angiogenic diseases, including hemangiomas, and the unpredictability of whether an effective amount of angiostatin could be produced in the treated patients, even with a maximum increase in the amount of administered plasminogen activator, for reasons set forth above, and in previous Office actions, 2) the lack of adequate disclosure in the specification, and 3) in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

June 13, 2005